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Pramlintide Acetate: A Brief Review

Indications

Pramlintide is indicated for the treatment of patients with type 1 and 2 diabetes mellitus (DM). In type 1 diabetes, it is indicated as an adjunct in patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy. In patients with type 2 diabetes, it is indicated as an adjunct treatment in individuals who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy, with or without a concurrent sulfonylurea agent and/or metformin.[1]

Clinical Pharmacology

Pramlintide (AC137; 25,28,29 tripro-amylin) is a stable, nonaggregating synthetic analogue of endogenous amylin. Amylin is a 37-amino acid peptide secreted from pancreatic beta cells with insulin in response to nutrient intake. Pramlintide differs from amylin by only three amino acids.[2,3]

In healthy subjects, fasting amylin concentrations range between 4 and 11 pmol/L and increase 2- to 3-fold after the ingestion of a mixed meal.[2,4-6] In patients with type 1 DM, amylin concentrations are at the lower end of assay detection or are undetectable and do not increase after meal ingestion.[2] In patients with type 2 DM, amylin levels parallel insulin levels.[2] Plasma levels of amylin and insulin rise and fall in parallel in response to meals.[6]

Pramlintide reduces postprandial hyperglycemia through several mechanisms, including delay of gastric emptying, prevention of the postprandial rise in plasma glucagon, and centrally mediated modulation of appetite, resulting in decreased caloric

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Update on Intravenous Immune Globulin Products

The commercial supply of intravenous immune globulin (IVIG) products on a national basis has become problematic over the last year. The Clinical Center (CC) Pharmacy, like other institutional pharmacies throughout the country, is experiencing difficulty procuring a consistent supply of IVIG. In May 2005, the formulary IVIG options were modified to include new products primarily based on product availability. Even since May, the CC Pharmacy has had to change IVIG brands a number of times to ensure that the CC has an adequate supply of IVIG for our patients. At this point, the poor market availability of IVIG products precludes having a limited list of consistent formulary IVIG products for prescribing as in the past. There are differences in IVIG product composition and recommended rates of administration that prevent ordering IVIG through a generic pathway. Prescribers should check with the CC Pharmacy (301-496-6551) to check on product availability and instructions on how to order the products that may be available. The limited market availability of IVIG products has also had a financial impact to the Clinical Center as the cost of IVIG products has been dramatically increasing. The average cost for IVIG per gram has risen from $30 in October 2004 to $82 currently (August 2005). The Pharmacy procurement staff is committed to ensuring an adequate supply of IVIG, but must also purchase from a reputable source. As in the past, it continues to be imperative that the utilization of IVIG be limited to appropriate clinical indications particularly given the limited supply and budgetary impact of these products.

intake and potential weight loss.[1] Subcutaneous (subQ) administration of pramlintide immediately before a meal reduced plasma glucose following the meal when used with regular insulin or rapid-acting insulin analogs. Reduced plasma glucose concentrations decreased the amount of short-acting insulin required and also limited glucose fluctuations over a 24-hour period. When administered with rapid-acting insulin analogs, plasma glucose tended to rise during the interval between 150 minutes following pramlintide administration and the next meal.[1] A single 120 mcg dose in patients with type 2 diabetes or 30 mcg dose in patients with type 1 diabetes administered 1 hour before an unlimited buffet meal resulted in a 23 and 21 percent reduction, respectively, in total caloric intake without reducing meal duration.[1]

Pramlintide delays gastric emptying associated with vagal stimulation; in animal models, it is secondary to centrally mediated activity.[2,7] In healthy subjects, gastric emptying half-time was increased from 112 minutes on placebo to 169 minutes with pramlintide 30 mcg and 177 minutes with pramlintide 60 mcg.[2] At 120 minutes after meal ingestion, 47 percent of the meal was retained with placebo compared with 72 percent retained with pramlintide 30 mcg.[2] Small bowel and colonic transport are not affected.[2] The effect on gastric emptying lasts for approximately 3 hours after pramlintide administration.[1]

In men with type 1 DM, administration of pramlintide 25 mcg/h as a 5-hour intravenous (IV) infusion started 1 hour before a radiolabeled test meal delayed emptying of liquid and solid components of the meal. For the liquid component, the median time taken for 10 percent of the isotope to empty was 7.5 minutes with placebo and 69 minutes with pramlintide ($P = 0.008$). For the solid component, the median time taken for 10 percent of the isotope to empty was 44.5 minutes with placebo and 150 minutes with pramlintide ($P = 0.016$). The median gastric emptying half-time was 45 minutes for the liquid component and 163.5 minutes for the solid component after placebo. Gastric emptying was monitored for 240 minutes after the test meal, but did not allow calculation of the gastric emptying half-time following pramlintide administration because of the prolonged delay in gastric emptying.[8] Similarly, pramlintide 30, 60, and 90 mcg doses administered subQ delayed gastric emptying in men with type 1 diabetes. Compared with placebo, all three doses delayed emptying of the solid component of a meal administered at the time of study drug administration. The mean gastric emptying half-time for the solid component was 128.6 minutes with placebo, compared with 187.2 minutes with pramlintide 30 mcg, 200 minutes with pramlintide 60 mcg, and 214.5 minutes with pramlintide 90 mcg ($P < 0.004$). Pramlintide had no effect on gastric emptying of a second meal administered 4 hours after the first meal.[9] Pramlintide 30 and 60 mcg subQ three times daily produced similar delays in gastric emptying in subjects with type 1 and type 2 diabetes. The mean gastric emptying half-time was increased from 91 minutes with placebo to 268 minutes with the 30 mcg dose and 329 minutes with the 60 mcg dose ($P < 0.01$).[10]

In patients with type 1 DM, administration of pramlintide 50 mcg/h as a 5-hour infusion reduced postprandial plasma glucose concentrations following a typical American breakfast and following a standardized Sustacal meal (350 kcal) challenge. Following the Sustacal meal challenge, the mean area under the glucose curve, corrected from baseline, was reduced from –1,869 mg/dL•min during placebo infusion to –28,872 mg/dL•min during the pramlintide infusion ($P = 0.0015$). Following the typical meal, the mean area under the glucose curve above baseline was –4,369 mg/dL•min during pramlintide infusion and 8,540 mg/dL•min for placebo ($P < 0.02$). Pramlintide infusion did not reduce plasma glucose exposure following administration of an IV glucose load.[4]

Pramlintide also has been shown to reduce postprandial hyperglycemia with subQ administration in 84 patients with type 1 DM. Patients received pramlintide 30, 100, 300 mcg, or placebo by subQ injection 30 minutes before meals for 14 days. A Sustacal meal (360 kcal) challenge was performed on days 1 (before treatment), 7, and 14. The total plasma glucagon response to the caloric challenge was reduced compared with placebo ($P < 0.05$); 1,397 pg•min/mL with placebo compared with 238 pg•min/mL with pramlintide 30 mcg, 576 pg•min/mL with pramlintide 100 mcg, and 48 pg•min/mL with pramlintide 300 mcg. The fasting glucose concentrations were similar for all three groups, ranging from 156 to 196 mg/mL, while the glucose levels 30 minutes after the meal showed a higher rise with placebo than any of the three doses of pramlintide. The glucose area under the curve (AUC) during the first 3 hours after a meal was 409 mg/dL•min with pramlintide 30 mcg ($P = 0.0269$ compared with placebo), –727.8 mg/dL•min with pramlintide 100 mcg ($P = 0.0051$ compared with placebo), –3,403.8 mg/dL•min with pramlintide 300 mcg ($P = 0.002$ compared with placebo), and 7,760.6 mg/dL•min with placebo.[11,12] In similar studies, pramlintide also was shown to reduce basal and postprandial secretion of glucagon in patients with type 1 DM.[13,14] In conjunction with postprandial glucose-lowering effects in patients with type 1 diabetes, pramlintide also has been shown to reduce markers indicative of postprandial oxidative stress.[15]

In another similar study, subQ pramlintide 10, 30, 100 mcg, or placebo was administered four times daily 15 minutes before the morning, noon, and evening meals, and an evening snack in 168 patients with type 1 DM. During the study period, the patients continued their usual diet, insulin, and exercise regimens. A Sustacal meal challenge (7 kcal/kg) was administered on study day 1 (the start of a placebo lead-in period), day 9 (before starting therapy with pramlintide or placebo), day 15 (the seventh day of study drug administration), and day 23 (the end of the study). Results were available for 159 patients evaluable for a 24-hour plasma glucose profile and 145 patients evaluable for the Sustacal meal challenge. Plasma glucose AUC following the Sustacal meal challenge after 1 and 2 weeks of study drug administration (days 15 and 23) was compared with the plasma glucose AUC following the placebo lead-in period (day 9). Compared with placebo and pramlintide

10 mcg, glucose AUC was reduced in the pramlintide 30 and 100 mcg groups. Plasma glucose AUC results are summarized in Table 1. Twenty-four hour plasma glucose profiles also revealed a 1.9 mmol/L mean reduction in plasma glucose in the pramlintide 30 mcg group compared with a 0.03 mmol/L reduction in the placebo group after 2 weeks of therapy. A similar trend was observed in the 100 mcg group. Seventy percent of patients (28 of 40) in the 30 mcg group had an at least 0.8 mmol/L reduction in mean glucose from baseline ($P = 0.003$).[16] Similar results were reported in a study enrolling 19 subjects with type 1 diabetes treated with regular insulin and 21 subjects with type 1 diabetes treated with insulin lispro. Pramlintide 60 mcg administered in conjunction with meals lowered total postprandial glucose compared with placebo. Administration of pramlintide at or within 15 minutes of the start of the meal also lowered the initial postprandial insulin surge and was judged to be the optimal time of administration. [17] Similar results were also observed in a 4-week, double-blind, crossover, placebo-controlled study of pramlintide 30 mcg 4 times daily in 14 patients with type 1 diabetes. Pramlintide was associated with reductions in serum fructosamine, mean plasma glucose and postprandial glucose, and postprandial glucagon.[18]

Administration of pramlintide 30 mcg three times daily for 4 weeks in 18 patients with type 1 diabetes treated with an insulin pump resulted in a shift to more glucose measurements within the euglycemic range, despite a reduction in mealtime insulin dosages. After 4 weeks of therapy, postprandial glucose, glucagon, and triglyceride excursions were reduced 86, 87, and 72 percent, respectively ($P < 0.05$ vs baseline). The mean 24-hour glucose concentration declined from 168 to 151 mg/dL.[19]

A 5-hour pramlintide 100 mcg/h IV infusion decreased mean glucose, insulin, C-peptide, and lactate concentrations in the 4-hour period after a Sustacal meal challenge (kcal/kg) in 12 patients with type 2 DM managed with insulin. The mean plasma glucose concentration was reduced to 10.2 mmol/L during pramlintide infusion compared with 13.7 mmol/L during placebo infusion. In 12 patients with type 2 diabetes mellitus managed with diet and/or oral hypoglycemic medications, pramlintide infusion resulted in reductions in mean insulin, C-peptide, and lactate concentrations, but not glucose concentrations (9.5 mmol/L on pramlintide and 10.2 mmol/L on placebo), following a Sustacal meal challenge. However, glucose levels were reduced in the subgroup of patients in the diet and oral medication group with glycosylated hemoglobin (HbA_{1c}) levels greater than 8 percent at study entry. Postprandial glucagon levels were reduced during the pramlintide infusions compared with placebo in both the group treated with insulin and the group managed with oral medications. Overall, in the 24 patients, the mean plasma glucose concentration was reduced to 9.8 mmol/L during pramlintide infusion compared with 12 mmol/L during placebo infusion ($P = 0.0012$).[20,21] Pramlintide also reduced postprandial glucose when added to insulin lispro therapy in 19 patients with type 2 diabetes. Pramlintide 120 mcg administered at the start of the meal reduced the postprandial glucose excursion by 81 percent compared with placebo ($P < 0.05$).[22]

Table 1. Glucose AUC after Sustacal Meal Challenge in Patients with Type 1 Diabetes Mellitus Treated with Placebo or Pramlintide[16]

	Glucose AUC (mmol/L • min)	
Agent	***Week 1 (Day 15)***	***Week 2 (Day 23)***
Placebo	−22.1	+172.8
Pramlintide 10 mcg	−12.9	−149
Pramlintide 30 mcg	−755.6	−247.7
Pramlintide 100 mcg	−650.3	−303.1

Pramlintide has been shown to reduce the extent of glucose and lactate increases after a meal compared with placebo in healthy subjects.[3] Pramlintide does not change plasma glucose or endogenous glucose production in response to a glucagon challenge and does not appear to alter insulin-mediated glucose disposal.[23] In healthy subjects, pramlintide did not impair the symptom, catecholamine, or glucagon responses to insulininduced hypoglycemia.[24]

Pharmacokinetics

The absolute bioavailability of pramlintide after a single subQ injection is 30 to 40 percent. The peak concentration and total exposure as expressed as the AUC increased in a dose-proportional manner following administration of increasing doses into the abdominal area or thigh. Injection into the arm produced higher exposure with greater variability compared with administration into the abdominal area or thigh.[1] The thickness of the adipose layer, as assessed by body mass index or skin fold thickness, does not correlate with the relative bioavailability. The size of the needle does not influence pramlintide's bioavailability; 6 or 12.7 mm needles produced similar bioavailability.[1]

Pramlintide is about 60 percent bound to blood cells or albumin.[1] The half-life of pramlintide is approximately 48 minutes. Pramlintide is metabolized primarily by the kidney. Des-lys[1] pramlintide, the primary metabolite, is active and has a similar half-life.[1]

Following IV doses of 30, 100, and 300 mcg as 2-minute boluses or 2-hour infusions, peak pramlintide concentrations and the pramlintide AUC increased with increasing dose. Peak concentrations were higher following the bolus dose, but AUC, half-life, and clearance values were comparable. The distribution phase half-life is about 3 to 12 minutes. The terminal elimination half-life is 20 to 47 minutes. Steady-state volume of distribution is 56 L. Clearance is approximately 1 L/min.[3]

In patients with moderate or severe renal impairment (creatinine clearance 20 to 50 mL/min), pramlintide exposure was not increased and clearance was not reduced compared with subjects with healthy renal function. Studies have not been conducted in patients undergoing dialysis.[1]

The impact of hepatic insufficiency on the pharmacokinetics of pramlintide has not been evaluated. Because pramlintide is extensively metabolized by the kidney, hepatic impairment is not expected to affect blood concentrations of pramlintide.[1]

The pharmacokinetics of pramlintide have not been studied in geriatric patients. Age-related differences in pramlintide activity were not observed in geriatric patients treated with pramlintide in clinical trials (539 patients 65 years of age or older).[1] Pramlintide has not been studied in pediatric patients.[1]

Studies have not been conducted to assess the impact of gender on the pharmacokinetics of pramlintide. Gender-related differences in activity were not observed in clinical trials.[1] Studies have not been conducted to assess the impact of ethnicity on the pharmacokinetics of pramlintide. Differences in activity were not observed in clinical trials enrolling patients of different races/ethnicities (4,257 white patients, 229 Black patients, and 337 Hispanic patients).[1]

Comparative Efficacy

Type 1 DM

Pramlintide was evaluated in a double-blind, placebo-controlled study enrolling 215 patients 18 to 66 years of age with type 1 DM from 2 months to 43 years duration. Patients were administered pramlintide subQ 15 minutes before meals in one of four dosing regimens following completion of a 7-day placebo lead-in period: 30 mcg four times a day (before breakfast, lunch, dinner, and evening snack), 30 mcg three times a day (before breakfast, lunch, and dinner [BLD]), 30 mcg three times a day (before breakfast, dinner, and evening snack [BDS]), and 60 mcg twice daily (before breakfast and dinner) for 4 weeks. Patients were instructed to remain on their usual diets, insulin, and exercise regimens unless otherwise instructed by the investigator. Short-acting insulin dosages were increased by a mean of 3.6 units in the placebo group and were reduced by 1 to 2.3 units in the pramlintide groups. Results of this study are summarized in Table 2.[25]

A multicenter, double-blind, placebo-controlled study was conducted to evaluate the effects of concomitant pramlintide plus insulin therapy on metabolic control in patients with type 1 DM. Five hundred and eighty-six patients were treated with subQ insulin and pramlintide or placebo. Patients were randomized to treatment with pramlintide 60 mcg three times daily, pramlintide 90 mcg twice daily, pramlintide 90 mcg three times daily, or placebo three times daily for 26 weeks. The mean baseline HbA_{1c} was 9 percent. The HbA_{1c} change after 26 weeks was 0.1 percent with pla-cebo, –0.2 percent with pramlintide 60 mcg three times daily, –0.1 percent with pramlintide 90 mcg twice daily, and 0.1 percent with pramlintide 90 mcg three times daily. The mean change in body weight was 0.3, 1.6, –0.7, and 1.6 kg, respectively.[26]

A 2-year multicenter study was conducted to evaluate the long-term effects of pramlintide plus insulin on glycemic control in patients with type 1 DM. During the first year, patients (N = 480) were treated in a double-blind, placebo-controlled study with placebo or pramlintide 30 mcg four times daily. At week 20, pramlintide-treated patients were re-randomized to 30 mcg or 60 mcg four times daily if reductions from baseline HbA_{1c} were less than 1 percent at week 13. During the second year, patients were treated with pramlintide 30 to 60 mcg four times daily in an open-label extension study. The baseline HbA_{1c} was 8.9 percent in the placebo group and 8.7 percent in the pramlintide group in the double-blind portion of the study. The mean HbA_{1c} at the end of the first year was reduced 0.39 percent with pramlintide and 0.12 percent with placebo ($P = 0.0071$). An HbA_{1c} less than 7 percent was achieved by 25 percent of patients in the pramlintide group compared with 11.3 percent in the placebo group ($P = 0.01$) and an HbA_{1c} less than 8 percent was achieved by 58.6 percent of patients in the pramlintide group compared with 35.1 percent in the placebo group ($P = 0.04$). Of the 342 patients who completed the first year of the study, 236 opted to participate in the openlabel study, including 126 previously treated with pramlintide. The reduction in the HbA1c during the first year (0.43 percent) in those treated with pramlintide was maintained throughout the second year of the study (0.35 percent). A sustained reduction in mean body weight was observed in the pramlintide group (approximately 0.5 kg), while patients in the placebo group experienced an increase in mean body weight (approximately 1 kg).[27,28]

Table 2. Changes In Monitored Parameters from Baseline after 4 Weeks of Pramlintide Therapy in Patients with Type 1 Diabetes Mellitus[25]

	24-Hour Mean Plasma Glucose (mcmol/L)	*24-Hour Glucose AUC (mcmol/L•min)*	*Serum Fructosamine (mcmol/L)*
30 mcg 4 times a day	–1.4a	–2,079.8[a]	–62[a]
30 mcg 3 times a day (BLD)	–0.03	–45.2	–43
30 mcg 3 times a day (BDS)	–0.1	–209.6	–47[b]
60 mcg twice daily	–0.9	–1,260.9	–46
Placebo	0.3	358.8	–29

[a]$P < 0.01$ vs placebo; [b]$P = 0.025$ vs placebo.
BLD = before breakfast, lunch, and dinner; BDS = before breakfast, lunch, and evening snack

Pramlintide also was assessed in a 1-year, randomized, doubleblind, placebo-controlled study enrolling 651 patients with type 1 diabetes. Patients received mealtime injections of placebo or pramlintide 60 mcg three times daily, 60 mcg four times daily, or 90 mcg three times daily, in addition to their insulin therapy, for 52 weeks. The 90 mcg dose was excluded from the efficacy analysis, resulting in inclusion of 479 patients treated with placebo or pramlintide 60 mcg in the efficacy analysis. Mean baseline HbA_{1c} was 8.9 percent. HbA_{1c} was reduced 0.29 percent from baseline in the patients treated with pramlintide 60 mcg three times daily ($P = 0.011$) and by 0.34 percent from baseline in the patients treated with pramlintide 60 mcg four times daily ($P = 0.001$), compared with a reduction of 0.04 percent from baseline in the group treated with placebo. Two to three times as many patients in the pramlintide group compared with the placebo group achieved an HbA1c less than 7 percent at any time during the study. Body weight was reduced from baseline to week 52 by 0.4 kg in the group treated with pramlintide 60 mcg three times daily ($P = 0.027$) or four times daily ($P = 0.04$), compared with a 0.8 kg weight gain in the placebo group.[29]

The prescribing information includes summarized data from three studies of pramlintide in patients with type 1 diabetes in which pramlintide or placebo was added to existing insulin therapies. Among the 1,179 pramlintide-treated patients in these studies, mean baseline HbA_{1c} ranged from 8.7 to 9 percent, mean age range was 37.3 to 41.9 years, mean duration of diabetes range was 15.5 to 19.2 years, and mean body mass index range was 25 to 26.8 kg/m^2. After 6 months of treatment, HbA_{1c} was reduced by a mean of 0.1 percent in the placebo group compared with a mean reduction of 0.43 percent in the patients treated with 30 or 60 mcg doses of pramlintide ($P < 0.05$). Weight increased 0.6 kg in the placebo group and was reduced 1.1 kg in the pramlintide group ($P < 0.05$).[1]

Type 2 DM

The long-term effects of pramlintide as an adjunct to insulin therapy in patients with type 2 diabetes were evaluated in a 52-week, double-blind, placebo-controlled study enrolling 656 patients. Mean patient age was 57 years, mean duration of diabetes was 12 years, mean body mass index was 34 kg/m^2, and mean HbA_{1c} was 9.1 percent. In addition to treatment with insulin, alone or in combination with sulfonylureas and/or metformin, patients were randomized to receive additional preprandial injections of either placebo or pramlintide 60 mcg three times daily, 90 mcg twice daily, or 120 mcg twice daily. Pramlintide or placebo was administered 15 minutes before major meals; for those receiving pramlintide twice daily the pramlintide was dosed before breakfast and dinner, with placebo administered before lunch to maintain blinding. Treatment with pramlintide 120 mcg twice daily was associated with a 0.68 percent reduction in HbA_{1c} at week 26 and a 0.62 percent reduction in HbA_{1c} at week 52 ($P < 0.05$ vs placebo). The HbA_{1c} reduction in the patients treated with the 90 mcg dose did not differ from that in the placebo group. An HbA_{1c} less than 8 percent was achieved in 46 percent of patients treated with pramlintide 120 mcg twice daily compared with 28 percent of placebo-treated patients ($P < 0.05$). An HbA_{1c} less than 7 percent was achieved in 12.2 percent of patients treated with pramlintide 120 mcg twice daily compared with 4.1% of patients treated with placebo. Patients treated with this dosage of pramlintide also experienced a 1.4 kg weight loss, compared with a gain of 0.7 kg in the placebo group at week 52 ($P < 0.05$).[30]

The prescribing information contains summary data from two double-blind, placebo-controlled studies in which patients with type 2 diabetes were treated with pramlintide 120 mcg in conjunction with insulin. Mean baseline HbA_{1c} was 9.3 percent for the placebotreated patients and 9.1 percent for those treated with pramlintide 120 mcg. At 6 months, the HbA_{1c} was reduced 0.17 percent in the placebo group and 0.57 percent in the pramlintide group ($P < 0.05$). The mean change in body weight at 6 months was a gain of 0.2 kg in the placebo group compared with a loss of 1.5 kg in the pramlintide group ($P < 0.05$). The dose of rapid-acting and short-acting insulin was increased 6.5 percent in the placebo group and reduced 3 percent in the pramlintide group at 6 months ($P < 0.05$). Similarly, the dose of long-acting insulin was increased 5.2 percent in the placebo group and reduced 0.2 percent in the pramlintide group ($P < 0.05$).[1]

The pramlintide 120 mcg dose also was assessed in an open-label study enrolling 166 patients with type 2 diabetes who were unable to achieve glycemic targets using insulin alone. In this study, pramlintide 120 mcg was administered with major meals. Insulin doses were adjusted based on pre- and postmeal glucose monitoring. Mean HbA_{1c} was 8.3 percent at baseline, mean age was 54.4 years, mean duration of diabetes was 13.3 years, and mean body mass index was 38.6 kg/m2. Pramlintide plus insulin treatment for 6 months resulted in a baseline-subtracted mean HbA_{1c} reduction of 0.56 percent. Baseline-subtracted mean weight was reduced 2.76 kg. Total insulin dose was reduced 6.4 percent; short-acting insulin was reduced 10.3 percent and long-acting insulin reduced 4.2 percent.[1]

Pramlintide also was assessed in a 52-week, randomized, placebo-controlled, double-blind study enrolling 538 patients with type 2 diabetes managed with insulin. Patients received placebo or pramlintide 30, 75, or 150 mcg three times daily with major meals. HbA_{1c} declined by 0.9 percent in the 75 mcg group and 1 percent in the 150 mcg group from baseline to week 13 ($P = 0.0004$ and $P = 0.0002$). From baseline to week 52, HbA_{1c} was reduced 0.6 percent in the 150 mcg group ($P = 0.0068$ vs placebo). HbA_{1c} less than 7 percent was achieved in 11.1 percent of patients treated with placebo, 12.7 percent treated with the 30 mcg dose, 13.4 percent treated with the 75 mcg dose, and 19.2 percent treated with the 150 mcg dose. Through week 52, body weight was reduced with all pramlintide dosages by approximately 0.5 to 1 kg, compared with an approximate 1 kg increase with placebo. A reduction in both HbA_{1c} and body weight occurred in 48 percent of pramlintide-treated patients compared with only 16 percent of placebo-treated patients.[31] When HbA_{1c} and body weight results from both

studies above in patients with type 2 diabetes were assessed in conjunction, comparable reductions in HbA_{1c} and body weight were evident in the three ethnic groups accounting for the majority of the study population (Black, white, and Hispanic).[32]

Pramlintide also was evaluated in a double-blind, placebo-controlled study enrolling 203 patients 25 to 78 years of age with type 2 DM managed with insulin for at least 6 months. Patients were administered pramlintide subQ 15 minutes before meals in one of four dosing regimens following completion of an 8-day placebo lead-in period: 30 mcg four times a day (before breakfast, lunch, dinner, and evening snack), 60 mcg three times a day (before BLD), or 60 mcg four times a day (before breakfast, lunch, dinner, and evening snack) for 4 weeks. Patients were instructed to remain on their usual diet, insulin, and exercise regimens unless otherwise instructed by the investigator. Serum fructosamine concentrations were reduced significantly from baseline in each of the pramlintide groups (17.5 mcmol/L in the 30 mcg four times daily group, 24.1 mcmol/L in the 60 mcg three times daily group, and 22.6 mcmol/L in the 60 mcg four times daily group, but not in the placebo group [3.5 mcmol/L]). Mean HbA_{1c} concentrations also were reduced from baseline to week 4 in each pramlintide group compared with placebo (0.53 percent in the 30 mcg four times daily group, 0.58 percent in the 60 mcg three times daily group, 0.51 percent in the 60 mcg four times daily group, and 0.27 percent in the placebo group). Fasting total cholesterol was reduced in the two pramlintide 60 mcg groups compared with placebo. Body weight also was reduced slightly (less than 1 kg) from baseline to week 4 in the two pramlintide 60 mcg groups.[7,25]

Contraindications

Pramlintide is contraindicated in patients with known hypersensitivity to pramlintide or any of the product ingredients (D-mannitol, acetic acid, sodium acetate), including the preservative metacresol; a confirmed diagnosis of gastroparesis; or hypoglycemia unawareness.[1]

Warnings and Precautions

The prescribing information for pramlintide contains a black box warning regarding an increased risk of insulin-induced severe hypoglycemia, particularly in patients with type 1 diabetes. Pramlintide therapy alone does not cause hypoglycemia, but it does increase the risk of insulin-induced severe hypoglycemia. Severe hypoglycemia associated with pramlintide occurs within the first 3 hours after pramlintide administration. To avoid increasing the risk of severe hypoglycemia upon initiation of pramlintide therapy, frequent pre- and postmeal glucose monitoring should be conducted and premeal dosages of short-acting insulin should be reduced 50 percent. Further insulin dosage adjustments may be necessary in the presence of other substances that lower blood glucose, including oral antidiabetic agents, angiotensin-converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase (MAO) inhibitors, pentoxifylline, propoxyphene, salicylates, and sulfonamide antibiotics.[1]

Proper patient selection is critical for the safe and effective use of pramlintide. Before initiating therapy, the patient's HbA_{1c}, recent blood glucose monitoring data, history of insulin-induced hypoglycemia, current insulin regimen, and body weight should be reviewed. Pramlintide therapy should only be considered for patients who have failed to achieve adequate glycemic control despite individualized insulin therapy and are receiving ongoing care under the guidance of a health care provider skilled in the use of insulin and supported by the services of a diabetes educator. Pramlintide therapy should not be considered for patients meeting any of the following criteria:[1]

- Poor compliance with current insulin regimen
- Poor compliance with prescribed self-blood glucose monitoring
- An HbA1c greater than 9 percent
- Recurrent severe hypoglycemia requiring assistance during the previous 6 months
- Presence of hypoglycemia unawareness
- Confirmed diagnosis of gastroparesis
- Need for medications that stimulate GI motility
- Pediatric patients

Pramlintide and insulin should never be mixed. Each should be administered as a separate injection. The pharmacokinetics of pramlintide were altered when mixed with regular, NPH, and 70/30 premixed formulations of recombinant human insulin immediately before administration.[1]

Local and systemic allergic symptoms have occurred with pramlintide. Patients may experience local redness, swelling, or itching at the injection site. Such reactions usually resolve within a few days to weeks. Potential systemic allergic reactions occurred in approximately 5 percent of patients with type 1 or type 2 diabetes treated with pramlintide, although such reactions also were reported in 5 percent of patients with type 1 diabetes and 4 percent with type 2 diabetes treated with placebo.[1]

Pramlintide is in Pregnancy Category C. Studies in perfused human placenta suggest pramlintide has a low potential to cross the placental barrier. In animal studies, however, increases in congenital abnormalities (neural tube defect, cleft palate, exencephaly) were observed in rats exposed to doses 10 and 47 times the exposure associated with the recommended human dose. Lower doses in rabbits had no effects on embryofetal development. Pramlintide should be used in pregnancy only if it is determined that the potential benefit justifies the potential risk to the fetus.[1]

It is not known if pramlintide is excreted in human milk. Pramlintide should be administered to a breast-feeding woman only if it is determined by the health care professional that the potential benefit justifies the potential risk to the infant.[1] Pramlintide therapy for 1 year in 12 patients with type 1 diabetes did not affect lumbar spine bone density or bone metabolism.[33]

Adverse Reactions

Adverse effects included nausea, vomiting, dyspepsia, anorexia, and headache (see Tables 3 and 4).[1,4,8,11,16,28-31,34,35] In clinical trials, nausea occurred in approximately one third to one half of patients treated with pramlintide.[1] With continued administration, nausea and anorexia were reported to occur less frequently.[1,5,16,34,35] The incidence and severity of nausea are lower if pramlintide is gradually titrated to the recommended dosage.[1]

Hypoglycemia has occurred with similar frequency in pramlintide- and placebo-treated patients with long-term therapy.[5,7,16,25,35] During the first 4 weeks of administration, severe hypoglycemic events occurred approximately 3 to 4 times more often in the pramlintide-treated patients than placebo-treated patients in one study involving patients with type 1 diabetes and another study enrolling patients with type 2 diabetes. The occurrence of severe hypoglycemic events declined after the first 4 weeks in both studies.[29,30] In longterm studies summarized in the prescribing information assessing pramlintide in type 1 diabetes, the incidence of severe hypoglycemia requiring medical assistance during the first 3 months of therapy was 3.3 percent in patients treated with placebo compared with 7.3 percent of patients treated with pramlintide when the insulin dosage was not adjusted. When the dosage of the insulin was adjusted during initiation of the pramlintide therapy, the incidence of severe hypoglycemia requiring medical assistance was 2.3 percent. In patients with type 2 diabetes, severe

Table 3. Common Adverse Reactions in Patients with Type 1 Diabetes Mellitus Treated with Insulin and Pramlintide 30 or 60 mg[1,*]

	Long-term, Placebo-controlled Studies		Open-label Clinical Practice Study
Adverse Event	***Placebo + Insulin (N = 538)***	***Pramlintide + Insulin (N = 716)***	***Pramlintide + Insulin (N = 265)***
Nausea	17%	48%	37%
Anorexia	2%	17%	0%
Inflicted injury	10%	14%	8%
Vomiting	7%	11%	7%
Arthralgia	5%	7%	2%
Fatigue	4%	7%	4.5%
Allergic reaction	5%	6%	Less than 1%
Dizziness	4%	5%	2%

*Incidence greater than or equal to 5 percent with pramlintide therapy and greater than placebo.

Table 4. Common Adverse Reactions in Patients with Type 2 Diabetes Mellitus Treated with Insulin and Pramlintide 120 mcg[1,*]

	Long-term, Placebo-controlled Studies		Open-label Clinical Practice Study
Adverse Event	***Placebo + Insulin (N = 284)***	***Pramlintide + Insulin (N = 292)***	***Pramlintide + Insulin (N = 166)***
Nausea	12%	28%	30%
Headache	7%	13%	5%
Anorexia	2%	9%	Less than 1%
Vomiting	4%	8%	7%
Abdominal pain	7%	8%	2%
Fatigue	4%	7%	3%
Dizziness	4%	6%	2%
Coughing	4%	6%	2%
Pharyngitis	2%	5%	3%

*Incidence greater than or equal to 5 percent with pramlintide therapy and greater than placebo.

hypoglycemia requiring medical assistance occurred in 0.7 percent of placebo-treated patients compared with 1.7 percent of pramlintide-treated patients during the first 3 months of therapy when the insulin dose was not adjusted. When the insulin dose was reduced at the time of pramlintide initiation, the incidence was 0.6 percent.[1]

Drug Interactions

No drug interactions have been reported, but pramlintide should be used with particular caution with other medications that can decrease blood glucose levels.[1]

Because of its effects on gastric emptying, pramlintide should not be used in patients taking other drugs that alter GI motility (e.g., anticholinergic agents, such as atropine) or agents that slow the intestinal absorption of nutrients (e.g., alpha-glucosidase inhibitors). Patients receiving such agents were excluded from pramlintide studies.[1]

Pramlintide may delay the absorption of coadministered oral medications. When rapid onset is a major determinant of effectiveness (such as analgesics), the agent should be administered at least 1 hour before or 2 hours after pramlintide.[1] The effects of pramlintide on the pharmacokinetics of acetaminophen as a marker of gastric emptying were assessed in patients with type 2 diabetes. Pramlintide did not alter the AUC of acetaminophen, but did reduce the peak concentration about 29 percent when administered simultaneously. The time-to-peak concentration also was increased depending on the time of acetaminophen administration relative to pramlintide. Pramlintide did not alter acetaminophen pharmacokinetics when acetaminophen was administered 1 to 2 hours before pramlintide. The time-to-peak acetaminophen concentration was increased when acetaminophen was administered simultaneously or up to 2 hours after pramlintide administration.[1]

Recommended Monitoring

Blood glucose and HbA_{1c} levels should be monitored periodically throughout therapy. Patients should be instructed to self-monitor blood glucose before and after meals and at bedtime.[1]

Dosing

The insulin dosage needs to be decreased in all patients when pramlintide is added to the drug regimen to reduce the risk of insulin-induced hypoglycemia. The insulin dosage can then be individualized based on blood glucose levels associated with the combination therapy.[1]

In patients with type 1 diabetes, pramlintide should be initiated at a dose of 15 mcg and titrated in 15 mcg increments to a maintenance dose of 30 or 60 mcg as tolerated. Preprandial and rapid- or short-acting insulin dosages should be reduced 50 percent. The dose of pramlintide should be administered immediately before major meals. The dosage of pramlintide may be increased to the next increment when no clinically significant nausea has occurred for at least 3 days.[1]

In patients with type 2 diabetes, pramlintide should be initiated at a dose of 60 mcg, with the dose increased to 120 mcg as tolerated. Preprandial and rapid- or short-acting insulin dosages should be reduced 50 percent. Pramlintide 60 mcg should be administered subQ immediately before major meals. The dose of pramlintide may be increased to 120 mcg when no clinically significant nausea has occurred for 3 to 7 days.[1]

Table 5. Conversion of mcg Pramlintide Doses to Insulin Syringe Unit Equivalents[1]

Dosage Prescribed (mcg)	*Increment Dose Using a U-100 Syringe (Units)*	*Volume (mL)*
15	2.5	0.025
30	5	0.05
45	7.5	0.075
60	10	0.1
120	20	0.2

Pramlintide should be administered subQ immediately before each major meal (250 kcal or more, or containing 30 g or more of carbohydrate). Pramlintide should be administered using a U-100 insulin syringe (preferably the 0.3 mL size). Table 5 contains the manufacturer's recommendation for conversion of the pramlintide dose to insulin syringe unit equivalents.[1] Each dose should be administered into the abdomen or thigh, with injection sites rotated. The site should be rotated so the same site is not used repeatedly and so that the injection site selected is distinct from the site chosen for the concomitant insulin dose. If a pramlintide dose is missed, an additional injection should not be given.[1]

If the pramlintide therapy has to be discontinued for any reason (e.g., surgery, illness), the dosage of pramlintide and/or insulin needs to be adjusted as if the patient had not previously been on pramlintide therapy.[1]

Product Availability

Pramlintide received Food and Drug Administration (FDA) approval in March 2005.[36] It is available as a clear, isotonic, and sterile solution for subQ administration. It is supplied in 5 mL vials containing pramlintide 0.6 mg/mL, metacresol 2.25 mg/mL as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. The solution has a pH 4.[1]

Unopened vials should be refrigerated (2° to 8°C [36°F to 46°F]) and protected from light. If a vial has been frozen or overheated, it should be discarded.[1] Opened (in-use) vials may be kept refrigerated or at room temperature for up to 28 days. Storage temperature should be kept below 25°C (77°F). Opened vials must be used within 28 days.[1]

Conclusion

Pramlintide may be useful in the treatment of some patients not achieving glycemic targets despite the use of individualized insulin therapy. Pramlintide is not a substitute for insulin but is complementary to insulin's action. Through a combination of mechanisms, it reduces postprandial and 24-hour plasma glucose concentrations. It improves glucose

control in patients with type 1 and type 2 diabetes. Patients receiving pramlintide therapy must be carefully selected and educated regarding the use of this medication and the need for close glucose monitoring.

Note

Pramlintide currently is not available on the Clinical Center Drug Formulary.

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